

# Cancer of the endometrium

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In 1995 the number of endometrial cancers diagnosed was estimated to be 4600, corresponding to a standardized incidence rate of 13.6 cases per 100 000 women in Europe. In the same year endometrial cancer was responsible for approximately 1200 deaths in France and it has become the third most common cancer in women after breast and colorectal tumours.

This document concerns the management of cancer of the uterine body but does not include sarcomas of the uterus.

These guidelines were validated in January 2000 and an update is planned in 2003.

## DIAGNOSIS

Hysteroscopy and transvaginal ultrasonography are the best initial examinations. The findings must be confirmed by biopsy (standard). Outpatient biopsy using Pipelle endometrial sampling is only useful if positive. It improves the specificity of a transvaginal ultrasound (standard). Fractional curettage gives the diagnosis in 95% of cases (standard). CA125 is of no diagnostic value (standard).

## STAGING

Although the primary treatment of endometrial carcinoma is usually surgery, preoperative imaging has an important role in the evaluation of operability (Figure 1):

- in rare cases where there is a contra-indication to surgery
- to detect locally advanced stages not suspected on clinical examination (for example in obese patients or in those difficult to examine)
- to assess iliac and/or para-aortic lymph nodes
- to assess pre-surgical prognostic factors (for example extension to the myometrium and to the cervix and thus the risk of nodal involvement).

Staging investigations must be planned by a multidisciplinary team (standard) and be adapted to the treatment strategy used by the team (standard). To evaluate local regional extension, a preoperative ultrasound, (which is not standard), is usually done (option). CT scanning is the best way to detect para-aortic nodal involvement (option). Literature review shows a small advantage for MRI over transvaginal ultrasonography for staging penetration of the myometrium. Ultrasonography is more readily available and less costly however (option). No examination is sufficiently sensitive and specific to distinguish between stage I and stage II disease. CA125 may predict for extra-uterine extension at levels  $>35 \text{ U ml}^{-1}$ .

## CLASSIFICATION

The pathological report must specify the precise origin of the tumour, its size and macroscopic features. It must document the extent of macroscopic infiltration of the myometrium, and if there is invasion of the cervix, parametrium and/or adnexae (standard). The diagnosis of endometrial carcinoma is based on histological examination. This determines both the histological type and grading of the tumour (standard). Immunohistochemistry and evaluation of hormone receptors may be carried out (option). In the case of diagnostic difficulty, immunohistochemistry is recommended. Use of the FIGO 1988 classification is standard (standard).

## PROGNOSTIC FACTORS

The following prognostic factors must be determined: FIGO classification, grade, differentiation, cervical invasion, depth of myometrial invasion, involvement of pelvic nodes, ovarian involvement, peritoneal cytology and histological type (papillary serous and clear cell carcinomas tend to behave more aggressively) (standard). A number of other prognostic factors may be considered: involvement of para-aortic nodes, initial CA125, hormone receptors, ploidy, growth factors (option). The use of FACS (fluorescent activation cytology scanning) is not currently recommended outside clinical research protocols. CA125 is correlated with prognosis but it is impossible to know if the assay provides any real benefit to the patient. It is of little value after treatment. The value of other markers is not yet clear.

## SURGICAL TREATMENT OF STAGE I AND II DISEASE

Surgery must always include the exploration, systematic inspection and palpation of the entire abdomen (standard) (Figure 2). All abnormal areas must be biopsied (standard). A sample must be taken for peritoneal cytology (standard, expert agreement). The hysterectomy must be at least total and extrafascial (standard, level of evidence B) with bilateral salpingo-oophorectomy (BSO) (standard, level of evidence B) (Figure 3). A modified radical hysterectomy (Piver type II) is undertaken for stage II cancers with macroscopic cervical lesions (standard) (Figure 4).

Lymphadenectomy can be undertaken by laparotomy or laparoscopy (option, level of evidence B). Hysterectomy can be by laparotomy, by the vaginal route or by laparoscopy (option, level of evidence B). An omentectomy is undertaken in the case of serous papillary forms (level of evidence B). When preoperative

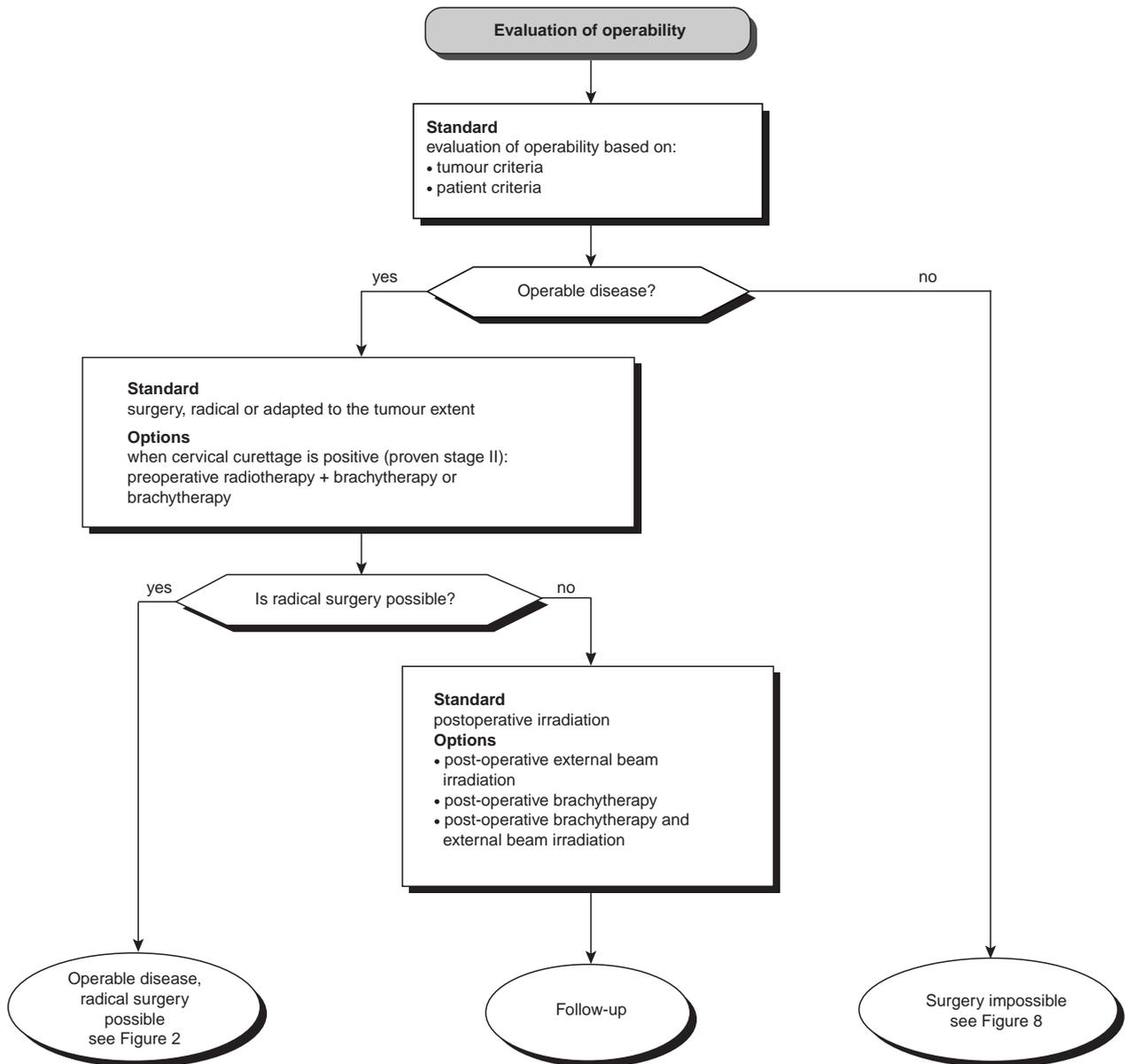


Figure 1 Evaluation of operability for cancer of the endometrium

staging has failed to show macroscopic invasion of the cervix, a modified radical hysterectomy (Piver type II) gives no added benefit over a simple hysterectomy.

**PLACE OF PELVIC LYMPHADENECTOMY IN STAGE I AND II DISEASE**

Pelvic lymphadenectomy can be done by laparotomy or by laparoscopy (options). Pelvic lymphadenectomy (option) should not be undertaken when there are bad prognostic factors (i.e. grade 3 pathology, greater than 50% infiltration of myometrium, stage II disease) that will necessitate postoperative radiotherapy (Figure 4). Pelvic lymphadenectomy is undertaken if the patient is of good performance status and if surgery is likely to be uncomplicated (Figures 3 and 4). Lymphadenectomy must not be undertaken in a patient of poor performance status; the uncertainty as to any

benefit on survival does not justify the operative risk. Pelvic lymphadenectomy is recommended by the International Federation of Obstetricians and Gynaecologists (FIGO) for the purposes of precise staging. Published data do not differentiate between the benefit of routine extended pelvic lymphadenectomy done in order to obtain optimum histopathological information, and a more selective approach whereby lymphadenectomy is only done in patients with a good prognosis. Randomized studies with comparable treatment in each sub-group are necessary to clarify this.

**PLACE OF PARA-AORTIC LYMPHADENECTOMY IN STAGE I AND II DISEASE**

Para-aortic lymphadenectomy does not constitute standard therapy in cancer of the endometrium. Excision of enlarged nodes can be

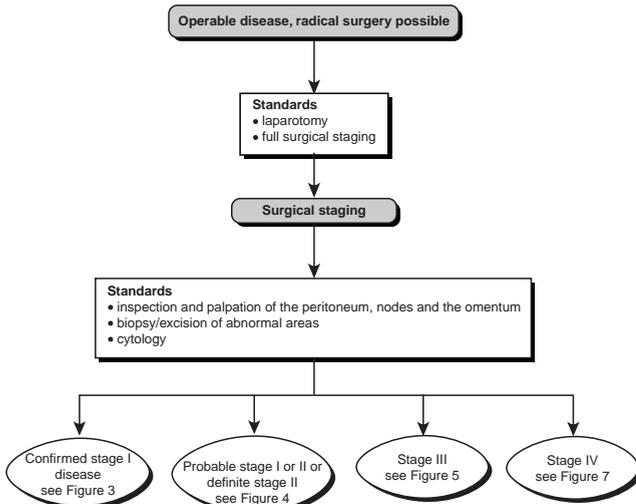


Figure 2 Management of operable disease: surgical staging

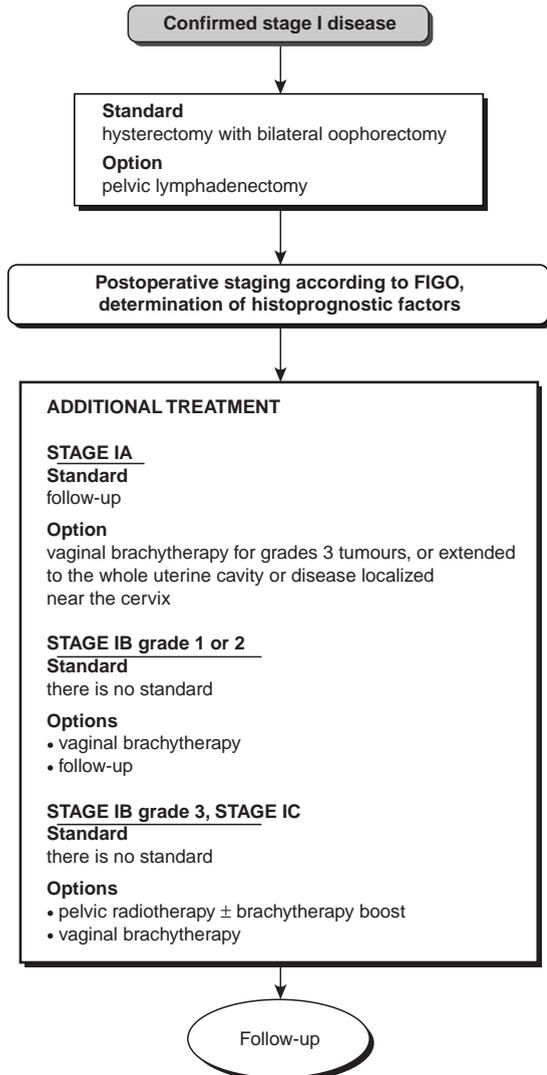


Figure 3 Treatment of stage I disease confirmed by surgical staging

an option. Para-aortic lymphadenectomy by laparotomy or laparoscopy (for those teams trained in this technique) can be

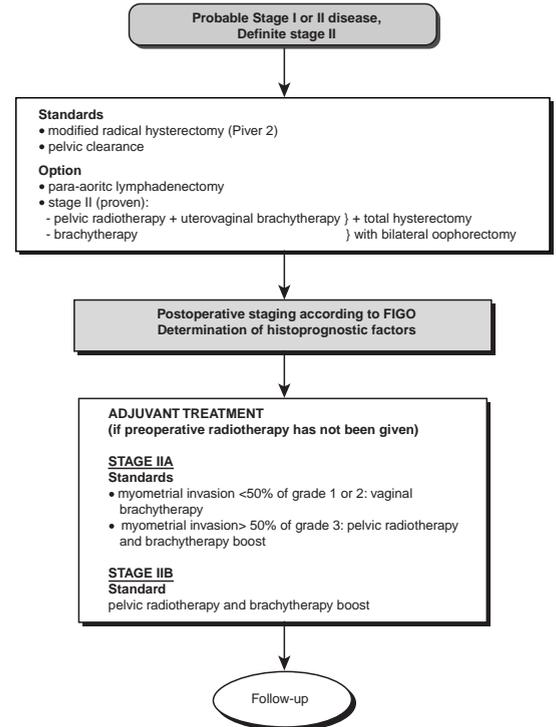


Figure 4 Treatment of stage I or II disease and confirmed stage II disease

undertaken (option) (Figure 4). Selective lymphadenectomy of enlarged para-aortic nodes is recommended. Routine para-aortic nodal clearance is not recommended. Although the recommendations of the Gynaecological Oncology Group (GOG) argue in favour of routine para-aortic lymphadenectomy, primarily for the purpose of staging, the following factors need to be taken into consideration:

- extent of the surgery
- presence of altered patient anatomy (due to age, or multiple concomitant disorders)
- rarity of isolated para-aortic invasion
- high predictive value of the involvement of pelvic nodes by para-aortic involvement
- correlation between nodal involvement and other main prognostic factors (invasion of the myometrium, ovaries, occult peritoneal disease, etc)
- controversy over the efficacy of adjuvant therapies (with the possible exception of occult nodal invasion).

The importance of these factors awaits confirmation from other studies. Experimental studies using injected coloured markers are underway to determine the pathways of uterine lymphatic drainage in order to facilitate selective lymphadenectomy.

**SURGERY FOR STAGES III AND IV**

Clinical stage III and IV cancers of the endometrium carry a bad prognosis. If the performance status of the patient permits it, cytoreductive surgery remains the best way to improve overall survival. Radical surgery must be the intention (standard) (Figures 1 and 5). Resection, as extensive as possible, followed by radiotherapy, or sub-optimal surgery followed by irradiation are possibilities

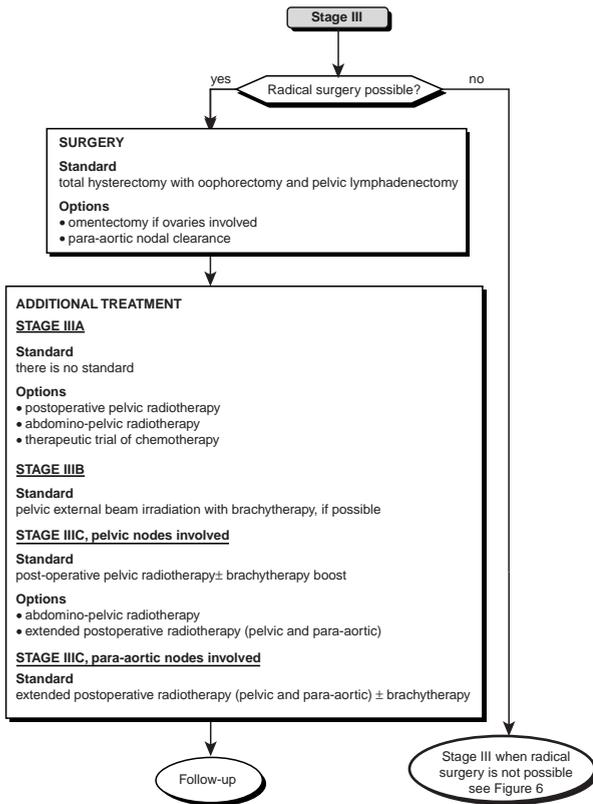


Figure 5 Treatment of stage III disease

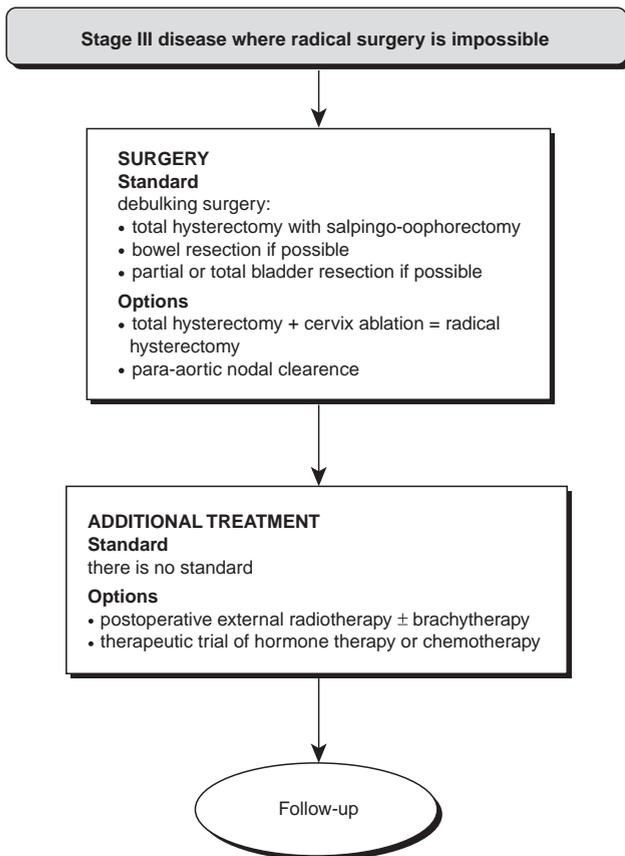


Figure 6 Treatment of stage III disease where radical surgery is impossible

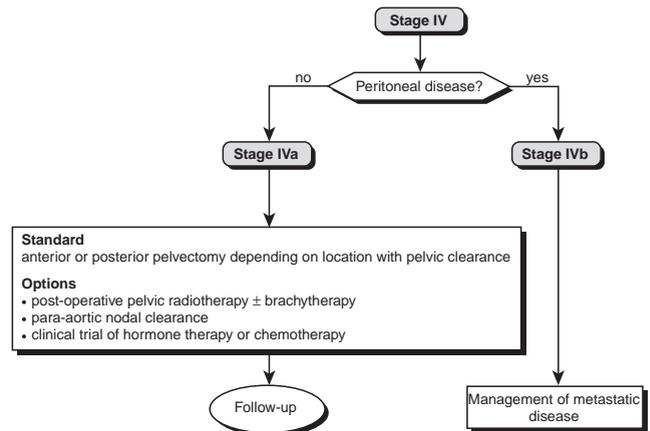


Figure 7 Treatment of stage IV disease

(options) (Figures 1, 5 and 6). It is recommended that cytoreduction surgery be carried out as follows: paramedial approach, total hysterectomy with BSO, colpectomy extending to adjacent healthy tissue, excision of pelvic and para-aortic nodes that are macroscopically involved, excision of free omentum in the case of ovarian involvement and location by clips of unresectable macroscopically involved nodes (Figures 5 and 6).

If the performance status of the patient is poor, a total hysterectomy plus BSO by an abdominal approach is preferable to treatment with radiotherapy alone.

**SURGICAL TREATMENT OF STAGE IV DISEASE**

Cytoreduction surgery is undertaken with a paramedial approach, total hysterectomy plus BSO, gut resection (if this allows for complete resection or if it is necessary to avoid obstruction) and partial or total bladder resection with urinary diversion (standard) (Figure 7).

**RADIOTHERAPY**

**Additional treatment for stage I disease after surgery**

For grade 1 and 2 stage IA tumours, follow-up alone is standard (Figure 3). Vaginal brachytherapy (option) can be undertaken for grade 3 stage IA disease, or for tumours localized adjacent to the cervix or involving the whole uterine cavity (Figure 3). For grade 1 and 2 stage IB tumours, the options are vaginal brachytherapy or follow-up alone (Figure 3). For grade 3, stage IB tumours and stage IC disease whatever the grade is or may be, there are two treatment options (Figure 3): external pelvic radiotherapy with or without a vaginal brachytherapy boost (level of evidence B) or vaginal brachytherapy (level of evidence C). Preoperative radiotherapy (either external or brachytherapy) is not recommended for stage I disease, as it cannot be planned according to specific histoprognostic factors of the tumour or to its exact extent and would therefore constitute overtreatment for some stage I tumours.

**Additional treatment for stage II disease**

When stage II disease has been proven by positive endocervix or cervix biopsy, there are two options; external radiotherapy with brachytherapy or brachytherapy followed by surgery, or surgery,

as primary treatment, followed by adjuvant radiotherapy given according to prognostic factors (Figures 1 and 4). If involvement of the cervix is not confirmed, primary surgery is recommended. Postoperative vaginal brachytherapy is given for stage IIA tumours if the penetration of the myometrium is less than 50% or if the tumour is grade 1 or 2 (standard) (Figure 4). When the myometrial penetration is more than 50% or for grade 3 disease, external radiotherapy with a brachytherapy boost has to be undertaken routinely (standard) (Figure 4). After primary surgery for stage IIB disease, postoperative external pelvic radiotherapy with a brachytherapy boost must routinely be undertaken (standard) (Figure 4).

### Additional treatment for stage III disease

For stage IIIA disease involving the ovaries only or with positive peritoneal cytology only, either external pelvic radiotherapy or abdomino-pelvic radiotherapy is advisable (option) (Figure 5). For stage IIIA tumours involving several extrauterine sites, standard treatment is abdomino-pelvic radiotherapy (standard), with additional medical treatment in certain patients (option). For stage IIIB tumours, postoperative external radiotherapy with brachytherapy (if possible) should be undertaken (standard) (Figure 5). For stage IIIC tumours, (involvement of pelvic nodes), standard treatment is external pelvic radiotherapy followed by a brachytherapy boost (standard) (Figure 5). Extended-field radiotherapy to para-aortic nodes is an option. If there are extra-uterine sites involved abdomino-pelvic radiotherapy is recommended (option). For stage IIIC tumours involving para-aortic nodes, extended external radiotherapy including pelvic and para-aortic nodes with or without brachytherapy is recommended (Figure 5).

### Treatment of inoperable disease

Standard treatment for inoperable stage I and II disease is external radiotherapy and brachytherapy (standard) (Figure 8). There are three possible options, radiotherapy alone, brachytherapy alone for stage I, or radiotherapy plus medical treatment (options). For patients with inoperable stage III or IV disease, treatment is often symptomatic, combining palliative external radiotherapy with medical treatment (Figure 8).

### Complications of radiotherapy

Late complications of external radiotherapy are most commonly gastrointestinal. Their frequency is correlated with the dose delivered to critical organs. The complications of postoperative brachytherapy include rectal injury and vaginal stenosis. These complications are closely linked to the dose delivered and to the length of vagina irradiated. If radiotherapy is the only treatment, both external radiotherapy and brachytherapy must be carefully planned to give good local control with the minimum of complications.

### ADJUVANT HORMONE THERAPY

There is no evidence to support the use of adjuvant hormone therapy (level of evidence A) Adjuvant hormonal therapy (option) should only be given within the context of a therapeutic trial (standard) (Figures 6, 7 and 8).

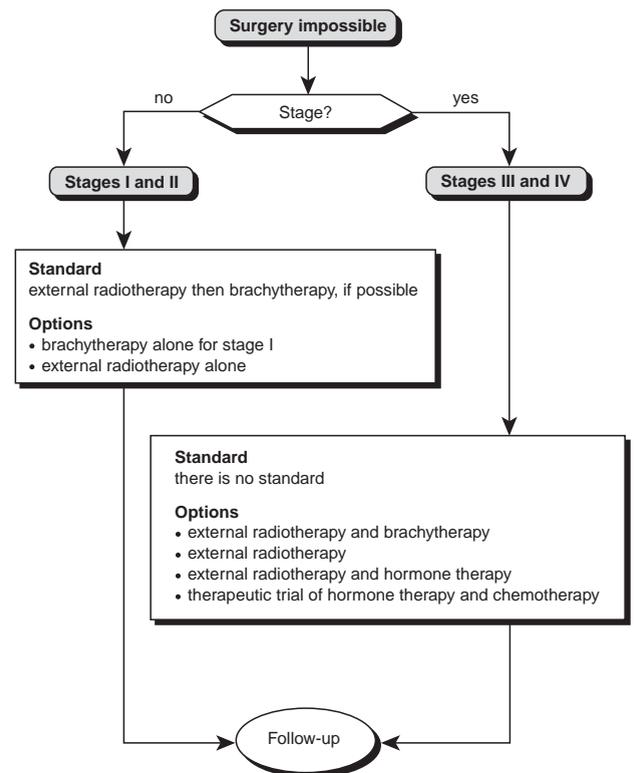


Figure 8 Treatment of inoperable disease

### CHEMOTHERAPY IN CANCER OF THE ENDOMETRIUM

Chemotherapy can be used for palliation (option). Doxorubicin and cisplatin are the drugs most commonly used. New Drugs are in the process of evaluation (option). The role of chemotherapy in metastatic cancer of the endometrium is limited in that the rate of response is less than 50%. Any benefit with respect to survival or quality of life has yet to be determined. No randomized study has compared chemotherapy with best supportive care.

### Adjuvant chemotherapy

No study has shown a benefit from adjuvant chemotherapy in cancer of the endometrium. Few randomized trials have been published; some have included only a small number of patients, others have not given final results. The inclusion criteria for trial entry are variable, making it difficult to compare results. There are prospective uncontrolled studies, but the small number of patients and the absence of randomization prevents any definitive conclusions to be made as to the efficacy of adjuvant chemotherapy. Adjuvant chemotherapy should be given within therapeutic trials (option) (Figures 6, 7 and 8).

### FOLLOW-UP

In the absence of specific symptoms or signs, follow-up is based on general and gynaecological examination (standard). The ideal timing of follow-up examinations has not been formally established; once every 6 months for the first 3 years then yearly is sufficient (standard). All patients presenting with symptoms

should have a full work-up (standard). There is no indication to carry out supplementary examinations looking for relapse or metastases in the absence of clinical signs. The CA125 assay is one examination which enables early diagnosis of recurrence, but this has no proven benefit with respect to prognosis and cannot be recommended as routine. It has not been demonstrated that hormonal replacement therapy in women of low risk with difficult menopausal symptoms increases the risk of recurrence or of metastases (option). Prospective studies are necessary before hormone replacement therapy can be recommended for women previously treated for carcinoma of the endometrium.

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